REMARKS

The Official Action dated May 26, 2006 and the references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, the Examiner indicates that claim 108 has been withdrawn from consideration for allegedly encompassing non-elected subject matter and claims 75 and 97 will only be examined to the extent that they read on the target gene being a plant viral gene. Additionally, the Examiner has indicated that claim 45 has been withdrawn from consideration. Accordingly, claims 33-36, 40, 41, 60-80 and 109-115 are currently being examined on the merits.

At page 3 of the Official Action, the Examiner has objected to the amendment filed on March 17, 2006 asserting that the amendment introduces new matter into the disclosure. Specifically, the Examiner contends that the phrase "corresponding complementary short sense RNA molecules" has no written support in the originally filed application. This assertion is contested herein and it is shown that explicit support for this phrase exists in the application as filed.

The Examiner has maintained the rejection of claims 33, 35, 40, 41, 75, 77, 78, 93-110 and newly rejected claims 34, 36, 60-74, 76, 79, 80, 83 and 111-115 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The claim amendments provided herein overcome this ground of rejection.

Claims 33-36, 76 and claim 111 stand rejected under 35

U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirements of the statute. The present claim amendments, coupled with the following remarks regarding the disclosure found in the application obviate this ground for rejection.

The Examiner has rejected claims 33-36, 40, 41, 60-80, 83, 93-107 and 109-115 as allegedly lacking sufficient written description in the specification. We demonstrate that this rejection is in error.

At page 12 of the Official Action, the Examiner has rejected claims 33, 35, 40, 111 and 112 under 35 U.S.C. §102(b) as allegedly anticipated by Waterhouse et al. PNAS 95:13959-13964 (1998). This ground for rejection must be reconsidered and withdrawn in light of the claim amendments provided herein.

The Examiner has also rejected claims 33-36, 40, 41, 60-62, 64-75, 77-80, 83, 93-101 and 111-114 under 35 U.S.C. §102(e) as allegedly anticipated by the disclosure in US Patent 6,506,559 and "evidenced by Applicants admitted state of the prior art." This ground for rejection must also be reconsidered and withdrawn in light of the claim amendments provided herein.

The foregoing objections and rejections constitute all of the grounds set forth in the May 26, 2006 Official Action for refusing the present application. Each of these objections and rejections are traversed and overcome for the reasons set forth below.

BRIEF OVERVIEW OF THE INVENTION AND TEACHINGS IN THE SPECIFICATION

Before responding to the various issues raised in the May 26, 2006 Official Action, Applicants wish to provide a brief overview of the invention disclosed in the present patent application.

The present inventors have described small RNA molecules of approximately 25 nucleotides which are the effectors of gene silencing and are claiming methods of use thereof. Three classes of RNA molecules are disclosed. These include short antisense RNA molecules (SARMs); short sense RNA molecules (SSRMs) and SRMs which contain both SARMs and SSRMs. Throughout the specification, the inventors refer to an about 25 nt species of RNA. The methods for purifying this species of RNA are provided at pages 6 and 7 of the specification. Notably, this purification method results in the obtention of SRMs as opposed to SARMs alone or SSRMs alone. Molecular characterization of these RNA molecules is provided in Example 1.

Example 1 describes silencing of a number of different target genes by a number of different mechanisms (co-suppression, transgene silencing, systemic induced gene silencing, and viral induced gene silencing), and shows in every case that an about 25 nucleotide RNA species is the common effector that correlates with silencing. In the example relating to co-suppression, silencing of the ACO gene in 5 lines of plants transformed with a cDNA encoding this enzyme is analyzed. The identification of the 25 nt species as being of both sense and antisense polarity is based upon hybridization of labeled sense and antisense

probes. At page 23, lines 29-33 these experiments are described as follows. "More specifically, the low molecular weight RNA and a 30 mer ACO antisense RNA oligonucleotide were fractionated, blotted and hybridized with either ACO sense RNA or antisense RNA transcribed from full length ACO cDNA." The results are discussed at page 23, lines 35-39 wherein the inventors disclose the following: *"A discrete ACO antisense RNA of 25 nucleotides (nt) was present in both PTGS lines but absent from non-silenced lines. 25nt ACO RNA of sense polarity and at the same abundance as the 25nt ACO antisense RNA was also present only in the PTGS lines."*

The silencing of PVX, GUS and GFP sequences by alternate mechanisms (i.e. transgene silencing, systemic induced silencing and viral induced silencing) were also correlated with the presence of an about 25 nt RNA species which was not detected in plants where silencing was not observed. The specification also discloses in Example 2, page 27-28, that the present invention is operative in widely divergent organisms, including plants, and nematodes.

Having identified 25 nt RNA species of both sense and antisense orientation as the effector of gene silencing, the inventors sought to protect their invention via the filing of the parent to the present patent application seven years ago. Identification of the 25 nt RNA species provided the skilled person with the common effector molecules that all in the field had been seeking, and made it a routine matter to then either sequence the isolated molecules or hybridize them to probes (either sense or antisense as taught in Example 1) corresponding to known sequences in the target gene. This characterization of the

effector molecules common to a variety of different forms of gene silencing in different organisms provides the necessary disclosure enabling those skilled in the art to analyze, produce and use the silencing agents encompassed by the claims. In a preferred embodiment, the silencing agent is an SRM comprising sense and antisense RNA molecules of approximately 25 nucleotides, which could base pair with the target nucleic acid (see further discussion of this below). Given the disclosure in the present application, and the recognition by those skilled in the art of gene silencing that Drs. Baulcombe and Hamilton were responsible for this seminal contribution to the field (see results from Google Scholar Search, attached hereto), Applicants respectfully submit that they are entitled to patent protection for this invention and further that the present application complies with all statutory requirements for issuance of these claims to patent.

THE AMENDMENT PRESENTED ON MARCH 17, 2006 DID NOT INTRODUCE NEW MATTER INTO THE DISCLOSURE OR THE CLAIMS

In the May 26, 2006 Official Action, the Examiner contends that the phrase "corresponding complementary short sense RNA molecules" comprises new matter and requires Applicants to cancel this subject matter from the claims and the specification. Notably, this language was also included in the new Abstract of the Disclosure provided to replace the original abstract as required by the Examiner. Applicants respectfully disagree with the Examiner's assertion that inclusion of this language introduces new matter into the specification and the claims.

It is expressly stated in the specification as filed that the SRMs of the invention comprise SARMs and SSRMs which are "collectively *…short complementary molecules which could base pair with the target RNAs*" (see page 2, lines 22-33). This disclosure provides explicit support, in relation to the mentioned short antisense RNA molecules (SARMs) for the language "complementary short RNA molecules".

At page 2, lines 14-20, the inventors describe the molecules they were the first to identify and characterize, i.e., "*a previously uncharacterised species of antisense RNA complementary to the targeted mRNA…of a uniform length, estimated at around 25 nucleotides [for which]…Corresponding sense RNA molecules were also detected.*" From this, it is clear that support exists for stating that "The SRMs are short complementary RNA molecules which include short antisense RNA molecules SARMs which could base pair with sense strands of the target and corresponding short sense RNA molecules, SSRMs which could base pair with the antisense strands of the target". In this context, it is unclear how this language could be interpreted in any way other than that short complementary (about 25nt long) antisense and corresponding sense molecules were identified as the effectors for efficiently and reliably achieving PTGS. This is further emphasized and made explicit at page 2, lines 21-26, where it is noted that "*There have been no previous reports of such short sense and antisense RNA molecules (hereinafter, collectively, SRMs*) that are detected exclusively in organisms exhibiting PTGS…" In sum, this language clearly teaches both that the sense and antisense molecules are complementary to each other and that the SRM must in some

way be able to base pair with the target RNA. Therefore, use of language in the claims and Abstract directed to "complementary short RNA molecules" which could hybridize with a target RNA cannot be considered new matter as *ipsisimus verbis* support for these claim limitations and language in the Abstract is found in the present specification. Applicants welcome the opportunity to discuss with the Examiner any proposed modification to the language utilized in the claims and Abstract to reflect this disclosure and support. However, inasmuch as the claims have been amended to recite that which is literally disclosed in the specification, it is urged that this objection cannot stand. Accordingly, Applicants submit that this basis for objection to the specification and claims must be reconsidered and withdrawn.

Claim 40, which was originally independent, has been amended such than it now depends on claim 33. Claims 35, 36, 37-39, 42-44, 71, 77, 78, and 100 have been cancelled. As mentioned previously, claim 33 has been amended to recite that which is literally disclosed in the specification and to specify that the SARMs and SSRMs hybridize to different strands of the target nucleic acid. This amendment cannot be considered to raise a new search issue as the terms SARMs and SSRMs were present in the initially examined claims. The newly added phrases make explicit that that the SARMs could hybridize to sense strands of the target and the corresponding SSRMs could hybridize to the opposite strand of the target as described in Example 1 of the specification. Applicants submit this subject matter should have already been thoroughly searched as the skilled person fully appreciates what is intended when one refers to molecules which are sense and antisense

to a particular double stranded nucleic acid target.

THE METES AND BOUNDS OF THE CLAIMS AS AMENDED ARE CLEAR TO ONE OF ORDINARY SKILL IN THE ART

The Examiner has maintained the rejection of claims 33, 35, 40, 41, 75, 77, 78 and 93-110 and newly rejected claims 34, 36, 60-74, 76, 79, 80, 83 and 111-115 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The claims have been amended to clarify the allegedly unclear subject matter.

The Examiner continues to contend that claims 33 and 40 are indefinite for inclusion of the phrase "silencing agent" despite the fact that he concedes that the specification expressly states that a silencing agent is preferably a SRM. Given this concession, the Examiner's further assertion "it remains unclear what else a silencing agent can be if it is not an SRM" is not understood by Applicants. Previously presented claims 33 and 40 clearly stated that the silencing agent comprises an SRM consisting of SARMs which can hybridize to sense strands of the target nucleic acid and SSRMs which can hybridize to antisense strands of the target nucleic acid. Thus, those skilled in the art would be fully apprised of the subject matter encompassed by this phrase. Nothing more is required under 35 U.S.C. §112, second paragraph.

Despite these arguments having full vitality, in order to address the concern expressed by the Examiner, Claims 33 and 40 have been amended omitting the phrase "silencing agent". Claim 33 is substantially simplified and recites that the method comprises introducing into an organism a SRM, as defined in the specification, and as discussed

above.

With respect to the open language "comprises", it would seem that the Examiner is seeking to limit Applicants to a claim in which the SRM and only the SRM is introduced to induce silencing. This is inappropriate from many perspectives. First, it is inappropriate as the specification supports a broader interpretation of the instantly claimed method. What the silencing agent may contain, for introduction into an organism or a cell to induce silencing, in addition to SRMs or sequences encoding SRMs is broadly described in the specification: see page 8, line 30 to page 9, line 4; page 9, line 36 to page 10, line 19; page 16, line 25 to page 20, line 14. This disclosure makes it clear that the "silencing agent" may comprise Agrobacterium, promoters, biolistic carriers and the like. Second, this attempt to limit the claims to a recitation of what else the silencing agent may contain aside from SRMs is contrary to common patent practice in which it is well accepted that so long as the active agent is recited in the claim, it is not necessary to limit the claim by defining any and all other possibilities for things that may be included with the active agent. Once again, however, to accommodate this stated concern by the Examiner, amended claim 33 is presented in which silencing agent is not mentioned and the open language "comprises" is referenced only to the method rather than that which is introduced (i.e. the SRMs) according to the method.

With respect to other related claims, it is noted that dependent claim 111 and 115 take this definition even further and recite that these molecules are present in equal abundance. Thus, Applicants submit that the skilled artisan would readily be apprised of the metes and bounds

of these claims. Literal support for this amendment to claim 33 can be found, for example, in Example 1, at page 23, lines 35 to 39. Additionally, Claim 35 has been cancelled thereby rendering the rejection of this claim moot.

As set forth in Applicants' previous response, the SRMs are RNAs which are *"short complementary molecules which could base pair with the target RNAs"* (see page 2, lines 28-33). In light of the definition of SRMs provided in the specification, the amendments to the claims provided herein clarifying that the SRMs consist of SARMs and SSRMs, and the biochemical characterization of the molecules via hybridization studies using sense and antisense probes corresponding to sequences from the target gene, it is respectfully submitted that the metes and bounds of claims 33 and 40 as amended would be clear to one of skill in the art. Reconsideration and withdrawal of this ground of rejection is therefore, respectfully requested.

At the top of page 5 of the Office Action, the Examiner states that it is "unclear how the same SRM (an individual nucleic acid molecule) can have both sense and antisense sequences." This is confusing to the Applicant, as the Examiner does acknowledge that the term "SRMs" is defined as collectively referring to **BOTH** sense and antisense RNAs of approximately 25 nt. Thus, by its very definition, the term SRM encompasses both sense and antisense sequences.

Next, the Examiner asserts that the specification does not define SRMs as being double stranded molecules. In fact, however, the specification as discussed above clearly discloses that the identified molecules are short antisense and corresponding short sense RNA molecules (page 2, lines

12-20). The specification also discloses that SRMs, collectively short sense and antisense RNA molecules (page 2, lines 22-26) are complementary molecules which could base pair with the target RNAs (page 2, lines 28-33). The specification further recites that known instances of silencing induced by dsRNA (albeit such instances relating to long dsRNAs) are related if not identical to the effects achieved and disclosed in the present specification (page 3, lines 23-26; page 11, lines 34-38) when using short complementary RNA molecules.

Moreover, Applicants submit that whether the 25 nt effector is double stranded or not in this context is purely semantic (see a more complete discussion of this point below in relation to the Waterhouse and Fire references alleged to anticipate the present claims; wherein data is presented which demonstrate that mixtures of sense and antisense RNAs of several hundred nucleotides which could base pair with a target were effective at inducing silencing, whether or not they were introduced as a preformed duplex molecule). The specification provides evidence that in silencing, without exception, in about the same abundance, (page 23, lines 38-39), short antisense RNA and corresponding sense RNA, which is also complementary to the antisense RNA (page 2, lines 28-33) is detected. Thus, short RNA molecules, at the natural temperature in which they are found in the cellular milieu, would hybridize with each other and form short double-stranded RNA molecules when not incorporated into the "PTGS machinery of the organism" (see the instant specification at page 9, line 30). As it turns out, that machinery has now been further elucidated and the antisense strand of a short dsRNA effector molecule is stripped from the duplex and utilized

as the sequence specific determinant for cleavage of target RNA. Claims 33, 40, 60, 93 and 102 to which the Examiner's objections are raised do not require that the SSRMs and SARMs present in the SRM be present in a double-stranded form. Because the full machinery and cellular mechanism required to effect silencing was not fully elucidated at the time, the specification and disclosure reflects the evidence on hand - that SRMs comprising complementary SARMs and corresponding SSRMs were required for efficient silencing to occur. It is not required by the specification or the claims that both sense and antisense molecules base pair with the target RNA, only that such molecules could base pair with the target RNA. Since both the sense and antisense molecules are encompassed by the term SRMs, if the target molecule is a mRNA, then the short antisense RNA (SARM) present in the SRM could hybridize with the target RNA, thereby meeting this claim requirement. In light of this explicit teaching, it is urged that it is incumbent on the Examiner to approve for patent the claims reflecting this specific disclosure, and if not, to explicitly and unequivocally demonstrate that the disclosure relied upon does not in fact support the claims. The Examiner has provided no such evidence contradicting this teaching in the specification.

The further assertion that there is no indication that SRMs can be interpreted to read on double stranded molecules is also in error. The disclosure expressly teaches at page 3, lines 10-26 and at page 11, lines 34 to 38, that PTGS in plants and dsRNA interference in nematodes are similar, if not identical processes. The distinction here being that, for the first time, the Applicants have demonstrated that the effector molecules common to PTGS in

plants, nematodes and higher organisms are short complementary sense and corresponding antisense RNA molecules (i.e. SRMs).

At page 6 of the Official Action, the Examiner asks the question: "If a SRM is a double stranded molecule, why would the specification teach that either a SARM or a SSRM could be used?" The Examiner further states that while Example 1 discusses the detection of SRMs in plants, "Nowhere is it stated that analyses were performed to detect small double stranded RNA".

In response, as mentioned above, the specification as originally filed discloses three classes of molecules, SARMs, SSRMs, and SRMs which comprise both SARMs and SSRMs. It is a well-settled premise in patent law that an inventor need not know exactly how his invention works mechanistically. See Parker v. Frilette, 174 U.S.P.Q 321,324 (CCPA 1972) ("[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice"). Applicants respectfully submit that the molecular mechanism underlying gene silencing is still a very active area of research 7 years after the filing date of the present application. Nonetheless, it is widely accepted in the art today that when a mixture of short complementary sense and antisense RNAs which could base pair with an appropriate region of a target, or when short double stranded RNA molecules, consistent with the present claims, are introduced into a cell efficient PTGS is induced, regardless of the mechanism by which their effect is achieved.

Briefly, as it is currently understood, gene silencing involves a complex of proteins and enzymes, known as the RNA Induced Silencing Complex, or "RISC" which binds to one

of the strands of a short RNA duplex and utilizes that strand to guide sequence specific cleavage of a target RNA molecule. Notably, this guiding molecule, which is incorporated in the RISC can base pair with the target gene. Short single stranded RNA molecules (e.g., SARMs) may be taken up by a RISC complex to effect cleavage of a target RNA, but the efficiency of this process is much lower than when both the sense and antisense are present (see Waterhouse and Fire, discussed below) or when a short double stranded RNA is present for take-up by or assembly into the RISC complex. See Martinez et al., Cell 110:563-574, (2002; submitted with the response to the previous Official Action) who showed that short dsRNA reconstitutes RISC at a concentration that is about 10 to 100 fold lower than that required for a short single stranded RNA. Which strand is selected by RISC for incorporation is under active investigation. It is essentially tautological to argue about whether it is the sense strand or the antisense strand that is incorporated, for, whichever strand is incorporated, if there is a target molecule with which that strand can base pair, then the RISC loaded with that short RNA becomes active to cleave the target molecule. Details of this mechanism are found in many current publications, including but not limited to those found in the above cited Martinez publication of record. (See, for example, page 563, right hand column, which confirms that RISC loaded with siRNA duplexes targets homologous sense as well as antisense single-stranded RNAs for degradation; Martinez at page 564 also notes that the "symmetric cleavage of sense and antisense target RNA by siRNA duplexes (Elbashir et al., 2001b, 2001c) may be explained by the presence of approximately equal populations of sense and antisense

strand-containing RISCs; further, at page 568, right hand column, Martinez notes "Therefore, a specific pathway exists which converts double-stranded siRNA into single-stranded siRNA containing RISC"; but see Martinez, figure 6, which also shows that SARMs are capable of reconstituting RISC). Accordingly, the present specification's teaching that SRMs as well as either SARM or SSRM could be used is consistent with the current understanding of the mechanism underlying PTGS induced by short RNA molecules. The biochemical analyses performed according to Example 1 indicate that **BOTH** SARMs and SSRMs were identified. See previous discussion of Example 1 above. It would be inconceivable for such strands to be present at the same abundance without any of those strands hybridizing to each other and forming duplexes. Thus, the Examiner's statement that "Nowhere is it stated that analyses were performed to detect small double stranded RNA" is inconsistent with the disclosure actually provided by the present specification.

The claims as originally filed also clearly encompass three classes of molecules, SRMS (which are collectively SSRMs and SARMs), SARMs and SSRMs. See original claims 1, 5, 6 and 26 which are reproduced below. Applicants contemplated and described three different classes of molecules which are effective to silence a target gene. Applicants' presentation of original claims 5 and 6 clearly support this position. If the SSRMs, SARMs and SRMs were identical, these claims would fail to further limit the subject matter of claim 1. Nor would claim 26 have been drafted to clearly indicate that the silencing agent may be **either** one or more SRMs **OR** an antisense molecule which can target a target gene.

ORIGINALLY FILED CLAIMS:

Original Claim 1. A method of screening for the occurrence of gene silencing in an organism, which method comprises the steps of

(i) obtaining a sample of material from said organism,

(ii) producing a nucleic acid extract from said sample,

(iii) analysing said extract such as to determine the presence or absence of short RNA molecules which are approximately 25 nucleotides in length(SRMs) in said nucleic extract, and

(iv) correlating the presence of said SRMs in the extract with the occurrence of gene silencing in said organism.

Original Claim 5. The method in accordance with claim 1, wherein the SRMs are short anti-sense RNA molecules (SARMs).

Original Claim 6. The method in accordance with claim 1, wherein the SRMs are short sense RNA molecules (SSRMs).

Original Claim 26. A DNA construct in which a promoter is operably linked to DNA for transcription in a host cell to generate a silencing agent for a target gene being selected from either:

(i) one or more SRMs, or

(ii) an anti-sense RNA molecule capable of targeting a region of said target gene selected in accordance with the method of claim 18.

It is further noted, in this context, that US patent 6,753,139, which issued from a common parent to the instant application, includes claims 1, 2, and 3, as follows:

1. A method of detecting the silencing of a target gene in a plant, wherein said silencing is initiated by introduction of an exogenous nucleic acid, which method comprises the steps of:

- (i) obtaining a sample of material from said plant,
- (ii) producing a nucleic acid extract from said sample,
- (iii) analyzing said extract such as to determine the presence or absence of short RNA molecules which are 21-25 nucleotides in length (SRMs) in said extract,
- (iv) characterizing any SRMs which are present in said extract such as to determine sequence identity or similarity with said target gene, and
- (v) correlating the presence of said SRMs having sequence identity or similarity with said target gene in the extract with the occurrence of gene silencing in said plant.

2. A method in accordance with claim 1 wherein the SRMs are short anti-sense RNA molecules (SARMs).

3. A method in accordance with claim 1 wherein the SRMs are short sense RNA molecules (SSRMs).

Clearly, therefore, the term "SRMs" encompasses short anti-sense RNA molecules **AND** short sense RNA molecules, and this is a point that the USPTO has already conceded as evidenced by the issued claims in US patent 6,753,139.

While different embodiments of the invention are described in the specification, the present claims are directed to methods for silencing a gene in an organism via the introduction of short complementary RNA molecules consisting of SARMs and corresponding SSRMs which could base pair with the target RNA) into a cell expressing the target gene to be silenced. Applicants note that it is wholly improper for the Examiner to seek to limit Applicants to certain embodiments of the invention when explicit disclosure consistent with a broader interpretation, or an interpretation which more closely reflects the subject matter the inventors regard as their invention is provided in the specification and in the original claims as filed. Additionally, Applicants reserve the right to file one or more continuing applications on these additional embodiments, including the introduction of SARMs alone to induce silencing.

With respect to the Examiner's stated observation that "both strands of a gene do not encode the gene product", this point is not disputed. However, as discussed above, in connection with the Martinez reference, this point is tautological. If a sense strand is present, then the SARM

of the SRM introduced into the organism is constituted into a RISC which effects sequence-specific cleavage of the sense strand, while, if an antisense strand is being transcribed, then the SSRM of the SRM introduced into the organism could base pair with that molecule and, constituted into a RISC, to effect the sequence-specific cleavage of the antisense strand. Once again, the teaching in the specification and the wording of the instant claims is consistent with the current understanding, years later, of the mechanism by which PTGS occurs. Reconsideration and withdrawal of this ground for rejection is therefore respectfully requested.

The Examiner also contends at page 6 that it is not clear how sense and antisense sequences can both be complementary to the same sequence. The qualification in the disclosure at page 2 that SRMs are short complementary molecules "which could base pair with the target RNAs" does not **require**, as the Examiner seems to be asserting, that the short complementary molecules both base pair with the target RNAs, or that they base pair with the target RNAs while in a double stranded form. Indeed, "could" which is the past tense of "can" is defined as 1: ability; 2: Possession of a specified power, right or means; i.e., the term is employed to indicate an ability to do something, not the requirement that the thing be done. The short sense RNA of the SRMs could base pair with the antisense strand of the gene, while the short antisense RNA molecule of the SRMs could base pair with the mRNA or sense strand of the gene. In fact, as mentioned above, it has been confirmed in the literature that short double stranded RNA molecules which comprise antisense strands that could base pair with a target molecule, in fact enter the RISC complex

described above wherein the short antisense RNA strand is stripped from its complement, and is utilized by the RISC to cleave the target RNA. This point is further emphasized in the specification which does not exclude the use of such short single stranded RNA, for example short single stranded antisense RNAs or SARMs. In this embodiment of the invention, if single stranded RNA is being utilized, it is preferable to use a SARM as opposed to a short sense RNA, e.g., a SSRNA, to induce silencing (something that has since been confirmed to occur).

Claim 60 has been amended to reflect the claim amendments to claims 33 and 40. Claims 77, 100 and 109 have been cancelled. Claims 93 and 102 have also been amended to further clarify the subject matter encompassed by these claims.

At page 6 of the Official Action, the Examiner has rejected claims 33 for lacking proper antecedent basis for the recitation of the targeted region in the last line. The claim has been amended to remove the phrase lacking proper antecedent basis, thereby rendering this rejection moot.

Claims 33, 40, 60, 93 and 102 are allegedly unclear for inclusion of the phrase "corresponding complementary". The Examiner alleges that "the specification does not explain what is meant by "corresponding"". It is further stated that "the specification does not state that the sense 25nt ACO RNAs were complementary to the antisense RNAs [and that, therefore] it is unclear exactly what is encompassed by the recitation, "corresponding complementary" in the claims, making the metes and bounds of the claim unclear".

Applicants strenuously disagree with the Examiner's

assertion that the term "corresponding" when referring to the SSRMs renders the claims indefinite. Indeed, US Patent '559 to Fire recites "…wherein the RNA is a double-stranded molecules with a first strand consisting essentially of a ribonucleotide sequence which **corresponds** to a nucleotide sequence of a target gene." The United States Patent office has issued no less than 120 patents wherein this term is utilized to refer to relationships between nucleic acid molecules. Attached hereto as Appendix A, is a listing of the claims from 30 of these patents. An objective review of this claim language reveals that those skilled in this art area conventionally use the term "corresponding" when referring to the relationship between nucleic acid molecules. As such, there is nothing whatsoever indefinite regarding what is encompassed by the statement that short antisense molecules and "corresponding sense" molecules were also detected. The skilled person would interpret this statement as encompassing molecules having a complementary sequence relationship, whether or not they in fact exist as double stranded molecules. Inasmuch as the term was found to satisfy the definiteness requirements for the cited 120 patents, and more particularly in the claims from 30 different patents discussed above and the '559 patent to Fire, Applicants submit that the USPTO has already determined that this term is clear to the skilled person and fully complies with the requirements of 35 U.S.C. §112, second paragraph. The Examiner is respectfully requested to consider the evidence presented in Appendix A. Notably, this evidence was not presented earlier because the issues relating to the term "corresponding" were initially raised in the Final Official Action.

The Examiner's attention is re-directed to the discussion provided above in connection with this topic in relation to the specification. Explicit support is found in the specification, all on the same page, (page 2), with respect to the nature of the SRMs - that antisense short RNAs were detected, that corresponding sense short RNAs were detected in equal abundance and that the nature of the SRMs is that they are short complementary molecules which could base pair with the target RNAs. Accordingly, Applicants reiterate that the present inventors have expressly described an about 25 nt RNA population comprising both sense and antisense molecules which, when present, effectively silence a target gene. The skilled person would readily appreciate that the phrase "corresponding" sense molecules refers to those molecules which could hybridize to antisense molecules of the same target. The Examiner may as well question what is meant by the word "sense", and obstruct issuance of a patent to the inventors on the basis of an epistemological argument about the meaning of that word. However, where, as here, the written description clearly teaches those of ordinary skill in the art that molecules, both of which are found invariably to be associated with silencing are of the same length, can base pair to a target sequence and are complementary, the ordinary meaning of the terms and language used has to be accorded sufficient deference as to permit the patent system to proceed. Accordingly, it is submitted that the metes and bounds of the teachings provided in the specification support a definite and clearly understood meaning for the phrase "corresponding". Reconsideration and withdrawal of this ground for rejection is respectfully requested.

Claims 75 and 97 have been amended to provide proper antecedent basis for the features recited therein.

In light of all the foregoing, it is respectfully submitted that the claims as amended fully comply with the requirements of 35 U.S.C. §112, second paragraph. Accordingly, the rejection of claims 33-36, 40, 41, 60—80, 83, 93-110, and 111-115 is improper and should be withdrawn.

THE CLAIMS AS AMENDED FULLY COMPLY WITH THE ENABLEMENT REQUIREMENTS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 33-36, 76 and 111 remain rejected as allegedly encompassing subject matter which was not enabled by the disclosure in the specification. Claims 35 and 36 have been cancelled, rendering the rejection of these claims moot.

The Examiner contends that the practice of the method of claim 76 requires undue experimentation as Applicants have not provided the "gene sequence of all plant parasite-resistance conferring genes and the parasites that each of these genes confers resistance against". In response, Applicants submit that a variety of plant resistance gene encoding sequences **WERE** known in the art at the time the present application was filed. Moreover, it is a well settled premise in patent law that a patent need not teach, and preferably omits, what is well known in the art. Lindemann Maschinenfabrik v. American Hoist and Derrick, 221 USPQ 481, 489 (Fed. Cir. 1984). Further, it should be emphasized and understood that the inventors have identified a common, broadly applicable method and effector molecules common to a wide variety of organisms and mechanisms of gene silencing (including, at least, co-

suppression, viral induced gene silencing, transgene induced silencing, and systemic induced gene silencing). The specific embodiment to which claim 76 is directed is a situation where the target gene is involved in parasite resistance. Based on the broad disclosure provided by this seminal contribution to the art, those skilled in the art are fully enabled to identify, for a given parasite, an appropriate target gene, and indeed an appropriate sequence in a target gene, for use as a silencing effector molecule. For example, as taught in the specification at page 3, lines 30-36, appropriate SRMs may be detected. Likewise, see the disclosure at page 9, lines 6-14, where there are provided methods for identifying a target region of a gene which it is desired to silence. Should the Examiner maintain the rejection of claim 76, Applicants stand ready to submit the gene sequences of parasite resistance conferring genes that were known to the skilled person as of the filing date of the present application.

The Examiner has rejected claim 33 for the recitation that the silencing agent base pairs with the target gene. At page 8 of the Official Action, the Examiner asserts, "However, neither the specification nor the prior art teach that PTGS occurs by base pairing of a nucleic acid with a gene within the genome of a plant cell or how a double stranded nucleic acid molecule can base pair with another nucleic acid molecule". In response, the Examiner is reminded that an inventor need not appreciate the molecular mechanism underlying his invention, he need only teach the skilled person how to make and use the invention. The explicit disclosure of an about 25 nt RNA species comprised of sense and antisense molecules which could hybridize with sense or antisense strands of a target is consistent with

the currently understood mechanism by which silencing utilizing short double stranded RNA effector molecules in fact occurs, as discussed in detail above. It is not required that the SRMs base pair with genomic DNA or any other molecule while the SRMs are in a duplex form.

It is further noted in this regard that despite the Examiner's asserted concern over how a duplex molecule according to the present invention could base pair with a target molecule, the Examiner does not refrain from citation of Fire, which exemplifies a duplex silencing agent of several hundred nucleotides and for which the US Patent Office has granted a patent for its use in inducing silencing of a gene through sequence-specific interaction with a target gene. Clearly, Fire fails to specify "how a doubled stranded nucleic acid molecule can base pair with another nucleic acid molecule."

The Examiner is incorrect that the definition of SRMs as comprising SARMs and SSRMs requires a duplex molecule to base pair with anything else. It is known that where a double stranded RNA molecule is provided, RISC strips out a single stranded molecule, either the SARM or SSRM to effect sequence-specific cleavage of a target RNA to which the RISC can base pair by virtue of the short sense or antisense RNA loaded therein. The Examiner's raising of the question of genomic DNA is spurious. This is being raised to suggest that if a both strands of the SRM are to base pair with the target then they must be base pairing with a DNA target. However, there is no mention whatever of genomic DNA in the claims, nor is there any requirement that both strands of the SRM base pair simultaneously with the target.

As an alternate formulation of the method encompassed

by this disclosure, Applicants proffer amended claim 33, which provides a method of silencing a gene utilizing short RNA molecules. In this way, the mechanistic concerns mentioned by the Examiner are avoided, while still taking into account the invention made by the present inventors.

Applicants are unclear as to the nature of the enablement rejection of claim 111. This claim was not included in the previous rejection under 35 U.S.C. §112, first paragraph. Claim 111 depends from claim 33, and provides the additional feature that the SSRMs and SARMs are present in equal abundance. It is presumed, therefore, that the basis of this rejection is the same as that stated for claim 33, and to that extent, the response provided with respect to claim 33 is requested to be applied here. If this presumption is not correct, Applicants respectfully request that the Examiner provide the reasoning for the rejection of this claim in the next Official Action. In addition, as it appears that this is a new ground for rejection, the action to which this amendment responds should not have been made final.

In light of the foregoing remarks and claim amendments, the rejection of claims 33-36, 76 and 111 under 35 U.S.C. §112, first paragraph is untenable and should be withdrawn.

CLAIMS 33-36, 40, 41, 60-80, 83, 93-107, AND 109-115 AS AMENDED FULLY COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected the aforementioned claims asserting that the subject matter encompassed thereby was not described in such a way as to convey to the skilled

person that the present inventors were in possession of the invention at the time the present application was filed. Applicants respectfully disagree.

As mentioned above in connection with the rejection of the claims under 35 U.S.C. §112, second paragraph, the present specification discloses three distinct classes of molecules, i.e., SRMs which comprise **BOTH** SARMs and SSRMs. The Examiner's assertion that "There is no written descriptive support for the recitation "short RNA molecules comprising SARMs and corresponding complementary SSRMs in the original application" is flatly contradicted by the disclosure in the application. While the Examiner appears to acknowledge the disclosure at page 2 of the application, he further contends that the term "collectively is not synonymous with complementary". In response, it is noted that the specification explicitly states the nature of the SRMS, i.e., "short **complementary** molecules which could base pair with the target RNAs" (page 2, lines 30-32). Moreover, as discussed above, the term "corresponding" is conventionally used by the skilled person in this art area to describe a relationship between nucleic acid molecules and it is submitted that the specification is explicit on this point. The Examiner has provided no evidence whatsoever to refute this explicit disclosure found in the application. Once again, if the Examiner is objecting to the combining of the terms "corresponding" and "complementary", the claims have been amended to remove this combination and recite that which is literally disclosed in the specification. In any event, the Examiner's assertion that this recitation comprises NEW MATTER and that there is insufficient written description in the specification for the claims to recite SARMs and

SSRMs that are complementary is flatly contradicted, The Examiner at page 10 also seems to be seeking to put words into the specification requiring that additional written description be provided for "an individual short RNA molecule to comprise both SARMs and SSRMs, and for the SSRMs being complementary to the SARMs." What the Examiner means by "an individual short RNA molecule" is not clear. The instant specification does not require that the SARM and SSRM are all part of the same linear chain of nucleotides forming a single "individual short RNA molecule", although this is not excluded, and, precedent for such molecules as long hairpins exists in the known literature (see Waterhouse, Figure 1). Accordingly, with respect to what the instant specification teaches and what the instant claims seek to encompass, it is urged that the written description is fully adequate.

At the top of page 11, the Examiner states that "the specification does not state that the sense 25nt ACO RNAs were complementary to the antisense RNAs. In response, Applicants submit that the Examiner is not permitted to ignore specific teaching to this effect found in the specification at page 2, lines 30-33, and to assert that it is NEW MATTER to state in the claims that these molecules are complementary.

In response to the Examiner's contention at pages 11 to 12 of the instant Office Action, it is noted that at page 9 of the previous Official Action, the Examiner stated the following: "*…the specification while being enabling for the claimed method when the nucleic acid sequence that is introduced into the cell to cause PTGS is double stranded, or if singled stranded, is not as small as 30 nucleotides, does not reasonably provide enablement for the*

claimed method with single stranded SRMs." Applicants assert that this statement by the Examiner does in fact indicate that the Examiner previously acknowledged that the instant specification enables methods using double stranded SRMs as this is a direct quote from the Action.

At pages 11 and 12 of the present Official Action the Examiner emphasizes the disclosure relating to the SARM aspect of the invention, yet ignores other sections of the disclosure which clearly state that SRMs comprise **BOTH** SARMS and SSRMS. Moreover, the data presented in Example 1 clearly indicates that the about 25 nt SRM species are of sense and antisense polarity with respect to the target gene.

The Examiner further seeks to assert that a distinction is made in the specification between SRMs and dsRNA by quoting disclosure at page 12, lines 17-20 of the specification, which states "Since dsRNA induced PTGS is conserved between nematodes, protozoa and insects it is likely that these other organisms which support PTGS may be susceptible to SARMs." However, this disclosure does not at all support the point sought to be made by the Examiner. As discussed above, this is not at all consistent with the disclosure of the present invention, or the current understanding of the mechanism underlying PTGS. First, at page 11, lines 34-38 of the specification, it is disclosed that "As shown in the Examples below, it appears that the same type of SARMs are present in *C. elegans* which are undergoing PTGS induced by the ingestion of dsRNA. This implies that the mechanism of PTGS in plants and nematode is similar if not identical." This disclosure implies that since the present teaching of the invention shows that when SARMs are detected, corresponding complementary SSRMs are

also detected in the same amount, that the common effector of PTGS in plants, nematodes and other organisms are the SRMs as defined in this application. This has been widely validated in the literature as correct (see results from Google Scholar Search, attached hereto). Nematodes fed long dsRNA (that the dsRNA is a long dsRNA molecule stems from the fact that this is the form of RNA from *C. elegans* obtained from the Department of Embryology, Carnegie Institution of Washington, where Andrew Fire and his co-workers were attempting to elucidate the mechanisms of PTGS, see US Patent 6,506,559, which is also cited by the Examiner in the outstanding Office Action as discussed below, which requires that the region of complementarity with a target gene and the dsRNA be at least 25 nucleotides long) are rapidly found to contain SARMs and would, if tested, likewise be found to contain corresponding, complementary SSRMs. Accordingly, the actual import of the teaching provided with respect to dsRNA, *C. elegans*, and the mechanisms of PTGS at work is that the present inventors have identified the common effectors, namely the SARMs, the corresponding, complementary SSRMs, all of which are encompassed within the definition of the term SRMs (as discussed at length above). That SARMs are mentioned specifically again does not detract from the underlying teachings in the specification that SRMs comprise both SARMs and SSRMs, and that where silencing is occurring both SARMs and SSRMs are detected, even if one only or the other of these molecules is ultimately actively incorporated into the RISC.

Claims 77, 100 and 109 have been cancelled and therefore the Examiner's reiteration of the rejection of those claims as lacking an adequate written description is

not further addressed here, other than to say that in response, similar arguments to those outlined above would pertain.

Regarding the rejection of claims 75 and 97, the Examiner contends that the recitation "contained within said cell" is not supported by the disclosure in the specification. The Examiner's attention is respectfully drawn to page 25 of the specification wherein the 25 nt RNA species was isolated following synchronized PVX infection on leaves of untransformed *N. bethamiana*. Thus, the virus infected these cells and its expression was silenced by the 25 nt RNA silencing agent present therein. Accordingly, Applicants submit the Examiner's contention is in error.

The present claim amendments are all explicitly supported by the disclosure in the present application. It is without question that the present inventors were in possession of the methods presently claimed as of the filing date of this application. In light of the foregoing remarks and claim amendments, Applicants request that the rejection of the claims for allegedly lacking an adequate written description and containing new matter be withdrawn.

THE CLAIMS AS AMENDED ARE NOVEL OVER WATERHOUSE ET AL. AND FIRE ET AL.

The Examiner contends that the disclosure in Waterhouse et al. anticipates the subject mater of claims 33, 35, 40, 111 and 112. Applicants respectfully disagree. In order to render claims lacking in novelty, a prior art reference relied on in a §102 rejection must identically disclose each and every element claimed. It is respectfully submitted that the claims as amended are novel over Waterhouse et al.

Claim 33 as amended recites a method of silencing a target gene in an organism by post-transcriptional gene silencing (PTGS), the method comprising the step of introducing into the organism SRMs consisting of SARMs which could base pair with sense strands of the target gene and SSRMs which could base pair with antisense strands of the target gene, each of said SARMs and SSRMs being 25 nucleotides (25nt) in length minus 1, 2, 3, 4 or 5 nucleotides, and being effective to silence the target gene when present in a cell expressing said target gene. The other independent claims have been amended in a comparable fashion. The constructs disclosed by Waterhouse et al. contained the entire open reading frame of Pro in a sense or antisense orientation as well as a construct containing a stop codon within three codons of the initiation codon. As can be seen from figure 3 of the cited publication, the Pro sense transcript and the antisense transcript are each between about 240 and 1200 base pairs in length. These transcripts when they base pair with each other intracellularly, form a duplex RNA that is on the order of between about 240 and 1200 base pairs in length. As is known from other literature, (see discussion of Fire's US Patent below), long double stranded RNA induces PTGS. However, as it has come to be understood today, long double stranded RNA is cleaved by the cellular machinery into short dsRNA, and then single strands from such cleavage products are incorporated into RISC for sequence-specific degradation of target mRNA molecules. What Applicants teach is the direct introduction into an organism of short complementary sense and antisense RNA molecules which could base pair with a target, thus eliminating the need for long dsRNA to be cleaved to the size of the effector molecules

disclosed and claimed in the present application. Accordingly, inasmuch as this reference does not describe short complementary RNA molecules being introduced into an organism or a cell, it does not disclose a method which is identical to that presently claimed. Therefore, the anticipation rejection of claims 33, 35, 40, 111 and 112 based on this reference is inappropriate and should be withdrawn.

The Examiner has rejected claims 33-36, 40, 41, 60-62, 64-75, 77-80, 83, 93-101, and 111-114 as allegedly anticipated by the disclosure in US Patent 6,506,559 to Fire et al.

The Examiner states that Fire et al. teach a method which comprises "expressing or introducing into cells short RNA molecules that are complementary and are in sense and antisense orientation with respect to a portion of the target gene sequence. The RNA molecules are at least 25 nucleotides in length." (See Office Action of 26 May 2006, bottom of page 14).

A careful reading of Fire et al. reveals that, in addition to stating at column 8, lines 5 through 6 that "The length of the identical nucleotide sequences may be at least 25, 50, 100, 200, 300 or 400 bases". The Fire constructs exemplified contain hundreds of nucleotides, and none are about 25 or less in length (See Figure 4).

Purely in order to expedite prosecution in this case, however, claim 33 and the other independent claims have been amended to recite SRMs which are 25 **minus** 1, 2, 3, 4, 5 nucleotides in length. Therefore, as amended, the present claims are clearly free from Fire, which, in addition, teaches away from the subject matter directed to short complementary sense and antisense RNA molecules (which, as

explained and discussed at length above, will naturally have the propensity to form duplexes, particularly as they are present in the same abundance), which are shorter than 25 nucleotides, as encompassed by the present claims as amended.

Clearly, it cannot be reasonably maintained that Fire et al. disclose an identical method in light of the present claim amendments and foregoing remarks. Accordingly, Applicants' request that this rejection be reconsidered and withdrawn.

CONCLUSION

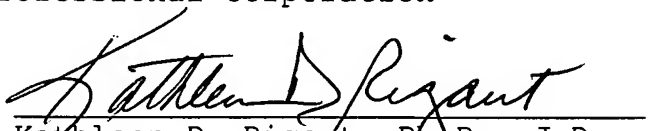
It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the rejections set forth in the May 26, 2006 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone or

in-person interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
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Enclosure: Results from Google Scholar Search
Listing of patent claims containing the term corresponding to describe relationships between nucleic acid molecules

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APPENDIX A

US Patent 7,029,854
8. A kit for identifying a sequence of a ***nucleic*** acid that is suitable for use as a substrate surface immobilized probe that can hybridize to two or more different target ***nucleic*** acids that ***correspond*** to the same genomic coding sequence, said kit comprising: (a) a computer readable medium according to claim 6; and (b) instructions for using said algorithm to identify said suitable sequence.

US Patent 6,852,494
6. An insoluble support comprising attached template ***nucleic*** acids, wherein (a) each attached template ***nucleic*** acids comprise a prokaryotic promoter sequence and a target sequence, (b) for each template ***nucleic*** acid, the promoter is located between the target sequence and the site that attaches the template ***nucleic*** acid to the support, (c) the template ***nucleic*** acids can be transcibed to produce RNA copies of each respective target sequence, and (d) the template ***nucleic*** acids is spaced firom the support by a nucleotide-free linker that includes an identical number of main chain atoms as a polyethylene glycol linker that has between 8 and 16 uniuts.

7. The support of claim 6 wherein the template ***nucleic*** acids ***correspond to nucleic*** acids in a biological sample.

8. The support of claim 7 wherein the template ***nucleic*** acids ***correspond*** to eukaryotic mRNAs.

US Patent 6,645,766

1. A method for producing an expression shuttle vector comprising a heterologous linear ***nucleic*** acid insert and capable of expressing said insert in a mammalian cell, comprising: (a) transforming yeast with a shuttle vector which shuttle vector comprises: (i) an origin of replication functional in yeast; (ii) a selectable gene functional in yeast; (iii) a promoter functional in a mammalian cell and capable of directing transcription of a polypeptide coding sequence operably linked downstream of said promoter; and (iv) an insertion site for an heterologous ***nucleic*** acid; wherein said insertion site is an homologous recombination site comprising a first ***nucleic*** acid sequence and a second ***nucleic*** acid sequence, which first and second ***nucleic*** acid sequences are contiguous, and wherein said first and second ***nucleic*** acid sequences taken separately ***correspond to a nucleic*** acid sequence at the 5' end of said heterologous ***nucleic*** acid and a ***nucleic*** acid sequence at the 3' end of said heterologous ***nucleic*** acid, respectively, and wherein said first and second ***nucleic*** acid sequences taken separately comprise ***nucleic*** acid sequences of from about 10 to about 100 nucleotides in length; (b) transforming yeast with a vector comprising an heterologous ***nucleic*** acid flanked by said first ***nucleic*** acid sequence and said second ***nucleic*** acid sequence; and (c) allowing said shuttle vector to recombine so as to insert said heterologous ***nucleic*** acid into said shuttle vector at said homologous recombination site.

US Patent 6,562,572
18. A method of identifying differentially expressed mRNA molecules, said method comprising hybridizing a population of mRNA-derived cDNA molecules from a first sample to a population of RNA molecules from a second sample; converting unhybridized, differentially expressed RNA molecules to subtracted cDNA molecules; and identifying said subtracted cDNA molecules by amplifying said subtracted cDNA molecules using a plurality of different primer pairs, each said primer pair comprising an initiation ***nucleic*** acid primer and a double restriction site primer, wherein said plurality of different ***nucleic*** acid primer pairs comprise at least four different initiation primers, wherein said at least four different initiation ***nucleic*** acid primers have the sequences 5'-R-S-ATG-A-3', 5'-R-S-ATG-C-3', 5'-R-S-ATG-G-3', and 5'-R-S-ATG-T-3', where R represents a restriction endonuclease recognition sequence, and S represents a degenerate nucleotide sequence from 1 to 10 nucleotides in length, and wherein said double restriction site ***nucleic*** acid primer comprises two restriction endonuclease recognition sequences, wherein said subtracted cDNA molecules ***correspond*** to differentially expressed mRNA molecules.

US Patent 6,509,153

10. A method of analysis of the toxic potential, in a human or murine cell, of a test compound, said method comprising: (a) separately contacting, under conditions allowing hybridization to occur, (i) labelled ***nucleic*** acid probes corresponding to RNA molecules (1) from human or murine cells treated with a candidate therapeutic molecule selected from a peptide, a polypeptide, a ***nucleic*** acid, a lipid, a carbohydrate, a chemical molecule and a plant extract, and (2) from untreated human or murine cells and (ii) a library of ***nucleic*** acids, wherein said library comprises, immobilized on a support, ***nucleic*** acid molecules comprising a sequence specific for genes or for splicing forms of genes, the expression of said genes or splicing forms being induced in a human or murine cell having a deregulated p53 gene expression or a deregulated p53 cell signalling pathway, and (b) analysing the hybridization profile between said probes and said library to determine the toxic potential of the candidate therapeutic molecule.

11. The method according to claim 1 or 10, wherein the test compound is an individual compound or is present in a mixture with other substances.

12. The method according to claim 1 or 10, wherein the ***nucleic*** acid library b) comprises ***nucleic*** acids having a sequence complementary to at least a portion of a gene that is induced by an increased wild-type p53 gene expression in a human or murine cell and ***nucleic*** acids having a sequence complementary to at least a portion of a gene that is spliced in a human or murine cell with increased wild-type p53 gene expression.

13. The method according to claim 1 or 10, wherein the treated or untreated human or murine cells are cell lines.

14. The method according to claim 1 or 10, wherein the treated or untreated human or murine cells are primary cultures.

15. The method according to claim 10, wherein the ***nucleic*** acid probes a) ***correspond*** to messenger RNA molecules from treated and untreated human or murine cells.

US Patent 6,479,652

1. A composition, comprising: a set of ***nucleic*** acids, comprising: a first subset of chemically synthesized oligonucleotide members which collectively ***correspond*** to at least a substantial portion of a first target ***nucleic*** acid; and, a second subset of chemically synthesized oligonucleotide members which collectively ***correspond*** to at least a substantial portion of a second target ***nucleic*** acid; wherein the first and second target ***nucleic*** acids encode non-identical proteins and comprise a plurality of regions of difference, and wherein the first and second subsets of chemically synthesized oligonucleotide members ***correspond*** to the regions of difference, and the first and second subsets are present in substantially non-equimolar amounts.

2. The composition of claim 1, wherein the members of the first subset which ***correspond*** to the regions of difference are present in the composition at a ratio of about 60 percent to about 40 percent members of the second set which ***correspond*** to the regions of difference, or higher.

3. The composition of claim 1, wherein the plurality of regions of difference comprise a plurality of non-overlapping subsequence regions of the first or second target ***nucleic*** acid.

11. The composition of claim 9, wherein the sequence diversity domains ***correspond*** to adjacent sequence regions on the first and second target ***nucleic*** acids when sequences corresponding to the target ***nucleic*** acids are aligned.

12. The composition of claim 1, wherein the oligonucleotide members of the first subset which ***correspond*** to the regions of difference are present in the composition at a ratio of about 70 percent to about 30 percent members of the second set which ***correspond*** to the regions of difference, or higher.

13. The composition of claim 1, wherein the oligonucleotide members of the first subset which ***correspond*** to the regions of difference are present in the composition at a ratio of about 80 percent to about 20 percent members of the second set which ***correspond*** to the regions of difference, or higher.

14. The composition of claim 1, wherein the oligonucleotide members of the first subset which ***correspond*** to the regions of difference are present in the composition at a ratio of about 90 percent to about 10 percent members of the second set which ***correspond*** to the regions of difference, or higher.

US Patent 6,448,010

1. A method for detecting a mutation in a target ***nucleic*** acid sequence that comprises: A. attaching oligonucleotide primers to a substrate, wherein the oligonucleotide primers have a sequence that is complementary to the target ***nucleic*** acid sequence, and wherein the oligonucleotide primers are grouped according to the identity of the first base which would be expected to be added to the primer through the process of primer extension; B. hybridizing to the oligonucleotide primers a sample ***nucleic*** acid sequence which possibly contains a mutation; C. extending each oligonucleotide primer by one base using a reaction mixture comprising labeled terminators and enzyme; and D. detecting a mutation in the sample ***nucleic*** acid sequence by detecting the presence of a labeled terminator which does not ***correspond*** to the identity of the base expected to be added to the primer through the process of primer extension.

US Patent 4,448,007

1. A cDNA library comprising at least 100 different cDNA molecules, said cDNA molecules comprising sequences that ***correspond*** to at least 100 different mRNA untranslated regions (UTRs) of unknown sequence, said UTRs being isolated and separate from adjacent mRNA coding regions.

2. A cDNA library, wherein said library is constructed by steps comprising a) purifying poly(A)+ RNA from total RNA; b) performing controlled, non-random enzymatic digestion of AUG sequences in the poly (A)+ RNA; c) purifying said digested RNA to obtain the fragments containing the 5' end sequences; and d) synthesizing cDNA from the purified RNA obtained in step (c); wherein said library comprises cDNA molecules, said cDNA molecules comprising sequences that ***correspond*** to different mRNA 5' UTRs, and said UTRs being isolated and separate from adjacent mRNA coding regions.

3. The cDNA library of claim 2, wherein said enzymatic digestion is carried out using RNase H.

4. A cDNA library, wherein said library is constructed by steps comprising a) purifying poly(A)+ RNA from total RNA; b) synthesizing ***nucleic*** acid heteroduplexes from said poly(A)+ RNA using degenerate primers that hybridize to the region surrounding and including the initiation codon, said heteroduplexes comprising the 5' end sequences of said RNA; c) purifying the heteroduplexes obtained in step (b) to obtain the fragments containing the 5' end sequences; and d) synthesizing cDNA from the purified heteroduplexes obtained in step (c); wherein said library comprises cDNA molecules, said cDNA molecules comprising sequences that ***correspond*** to mRNA 5' UTRs, and said UTRs being isolated and separate from adjacent mRNA coding regions.

US Patent 6,410,233

1. A method for identifying one or more cDNA molecules that ***correspond*** to one or more genes regulated by a transcription factor, comprising:

a) cross-linking at least one transcription factor to at least one ***nucleic*** acid molecule in at least one cell or at least one nucleus, forming one or more transcription factor-***nucleic*** acid molecule complexes;

b) fragmenting said at least one ***nucleic*** acid molecule to form one or more transcription factor-***nucleic*** acid molecule fragment complexes;

c) isolating one or more ***nucleic*** acid molecule fragments from said one or more transcription factor-***nucleic*** acid molecule fragment complexes to form one or more isolated ***nucleic*** acid molecule fragments;

d) combining said one or more isolated ***nucleic*** acid molecule fragments with either:

1) a ***nucleic*** acid sequence in a cDNA library of sequences known to be complementary to previously identified ***nucleic*** acid molecules, or

2) cDNA obtained by reverse transcription of a population of RNA molecules, to form a mixture comprising isolated ***nucleic*** acid molecule fragment/cDNA complexes;

e) amplifying one or more cDNAs in said isolated ***nucleic*** acid fragment/cDNA complexes using said one or more ***nucleic*** acid molecule fragments in said isolated ***nucleic*** acid fragment/cDNA complexes as primers to obtain one or more isolated cDNA molecules that ***correspond*** to one or more genes regulated by a transcription factor; and

f) identifying said one or more cDNA molecules that ***correspond*** to one or more genes regulated by a trascription factor by either:

1) sequencing said one or more cDNA molecules that ***correspond*** to one or more genes regulated by a transcription factor to obtain a sequence or sequences and comparing said sequence or sequences to the sequences of DNA molecules of known sequence to determine whether said one or more cDNA molecules has homology of greater than 70% with any of said sequences of DNA molecules of known sequence, or

2) hybridizing said one or more cDNA molecules that ***correspond*** to one or more genes regulated by a transcription factor to one or more ***nucleic*** acid molecules corresponding to known genes or ***nucleic*** acid sequences;

wherein the presence of a sequence or sequences having homology of greater than 70% or a hybridization results in the identification of said one or more cDNA molecules that ***correspond*** to one or more genes regulated by a transcription factor.

US Patent 6,391,582

We claim:

1. A method for forming an expression shuttle vector comprising an heterologous ***nucleic*** acid insert and capable of expressing said insert in a mammalian cell, comprising:

(a) transforming yeast with a shuttle vector which shuttle vector comprises:

(i) an origin of replication functional in yeast;

(ii) a selectable gene functional in yeast;

(iii) a promoter functional in a mammalian cell and capable of directing transcription of a polypeptide coding sequence operably linked downstream of said promoter; and

(iv) an insertion site for an heterologous ***nucleic*** acid;

wherein said insertion site is an homologous recombination site comprising a first ***nucleic*** acid sequence and a second ***nucleic*** acid sequence, which first and second ***nucleic*** acid sequences are contiguous, and wherein said first and second ***nucleic*** acid sequences taken separately ***correspond to a nucleic*** acid sequence at the 5' end of said heterologous ***nucleic*** acid and a ***nucleic*** acid sequence at the 3' end of said heterologous ***nucleic*** acid, respectively, and wherein said first and second ***nucleic*** acid sequences taken

separately comprise ***nucleic*** acid sequences of from about 10 to about 100 nucleotides in length;

(b) transforming yeast with a vector comprising an heterologous ***nucleic*** acid flanked by said first ***nucleic*** acid sequence and said second ***nucleic*** acid sequence; and

(c) allowing said shuttle vector to recombine so as to insert said heterologous ***nucleic*** acid into said shuttle vector at said homologous recombination site.

US Patent 6,303,295

What is claimed is:

1. A machine-implementable method for identifying selenoprotein coding sequences within a nucleotide sequence, said method comprising the steps of:

(a) translating in all possible reading frames the nucleotide sequence, wherein the step of translation is carried out treating UGA or TGA as a ***sense*** codon, to generate open reading frames (ORFs);

(b) identifying those ORFs having a plurality of UGA or TGA codons and which begin with a translation start codon selected from the group consisting of ATG or AUG or GTG or GUG as independent ORFs and identifying those ORFs which do not begin with a translation start codon selected from the group consisting of ATG or AUG or GTG or GUG as frameshift ORFs;

(c) identifying ORFs not containing internal in-frame UGA or TGA codons which ***correspond*** to known coding sequences;

(d) selecting those frameshift ORFs identified in step (b) which overlap a known coding sequence identified in step (c), and identifying frameshift ORFs wherein a -1 or a +1 frameshift sequence is located within overlapping of said coding sequences, wherein the -1 or +1 nature of the frameshift sequence matches the -1 or +1 nature of the frameshift required to change reading frame from that of the known coding sequence to that of the ORF identified in step (b) and identifying in the 3' untranslated region of the newly identified coding sequence, a SECIS element structure;

(e) as an alternative to step (d), selecting those independent ORFs identified in step (b) and analyzing for the presence of a SECIS element structure in the 3' untranslated region of the independent ORF, so that a selenoprotein coding sequence is identified;

whereby a frameshift-generated selenocysteine-containing fusion protein coding sequence is identified in step (d) or a selenoprotein coding sequence is identified in step (e).

US Patent 6,358,740

1. A method of recombining a plurality of sequence domains from a plurality of homologous or non-homologous parental ***nucleic*** acids, the method comprising:

recursively recombining the plurality of homologous or non-homologous parental ***nucleic*** acids, thereby providing a plurality of artificially recombined ***nucleic*** acids;

transcribing the plurality of artificially recombined ***nucleic*** acids, thereby providing pre-mRNAs each comprising a plurality of sequence domains which ***correspond*** to a plurality of different parental ***nucleic*** acid sequences; and,

alternatively splicing the pre-mRNAs to produce from each of the pre-mRNAs a plurality of different mRNAs comprising a plurality of different sets of sequence domains.

US Patent 6,323,030

1. A method of screening a ***nucleic*** acid library encoding enzyme variants for a desired property, the method comprising:

(a) providing a population of host cells comprising a recursively recombined ***nucleic*** acid library, wherein members of the library encode variants of an enzyme; and,

(b) screening the ***nucleic*** acid library by sorting the population of host cells, wherein the host cells are sorted by fluorescence activated cell sorting (FACS) into a plurality of collection regions by using detection of a signal produced by conversion of a substrate to a product.

2. The method of claim 1, wherein the recursively recombined ***nucleic*** acid library is produced by a method comprising:

(a) providing ***nucleic*** acid subsequences corresponding to at least one starting ***nucleic*** acid;

(b) hybridizing the subsequence ***nucleic*** acids to each other or to one or more additional ***nucleic*** acids;

(c) elongating the resulting hybridized subsequences to produce at least one recombinant ***nucleic*** acid, wherein said elongating comprises extending the hybridized subsequences with a first polymerase, denaturing the resulting extended hybridized subsequences, re-hybridizing the resulting single-stranded extended subsequences and extending the resulting re-hybridized extended sequences with the first polymerase or with a second polymerase to produce further extended sequences, and;

(d) recombining the further extended sequences with each other or with one or more additional ***nucleic*** acids to produce one or more of the members of the recursively recombined ***nucleic*** acid sequence library.

3. The method of claim 2, wherein producing the ***nucleic*** acid subsequences comprises cleaving at least two homologous ***nucleic*** acids.

4. The method of claim 2, wherein producing the ***nucleic*** acid subsequences comprises making synthetic oligonucleotides which ***correspond*** to subsequences of the at least one starting ***nucleic*** acid or to variants thereof.

5. The method of claim 1, wherein the recursively recombined ***nucleic*** acid library is produced by providing subsequences of at least one starting ***nucleic*** acid, hybridizing at least partially single stranded forms of the resulting subsequence ***nucleic*** acids to one or more additional at least partly single stranded ***nucleic*** acids, elongating the resulting hybridized subsequences with a polymerase, fragmenting at least one of the resulting elongated ***nucleic*** acids, and repeating the hybridizing and elongating steps with fragments of the elongated ***nucleic*** acids, thereby generating at least one recursively recombined ***nucleic*** acid, which at least one recursively recombined ***nucleic*** acid is a member of the recursively recombined ***nucleic*** acid library.

6. The method of claim 5, wherein producing the ***nucleic*** acid subsequences comprises cleaving at least two homologous ***nucleic*** acids.

7. The method of claim 5, wherein producing the ***nucleic*** acid subsequences comprises making synthetic oligonucleotides which ***correspond*** to subsequences of the at least one starting ***nucleic*** acid or to variants thereof.

US Patent 6,270,962

58. In the procedure for replicating a template nucleotide sequence containing trinucleotide repeats inhibitory to chain elongation, the improvement comprising adding an effective amount of a trimethylglycine to the reaction mixture of a Taq polymerase DNA replication reaction procedure wherein fewer different replication products which do not ***correspond*** to the template nucleotide sequence are produced than would be produced in the absence of trimethylglycine.

US Patent 6,229,066

1. An isolated ***nucleic*** acid polymer encoding a protein which exhibits cytokinin oxidizing activity, selected from the group consisting of:

(a) SEQ. ID NO. 1,

(b) a protein having an amino acid sequence which includes the amino acid sequence of SEQ. ID NO. 1, and

(c) a protein including an amino acid sequence wherein at least 65% of the amino acids of the amino acid sequence ***correspond*** to the amino acid sequence of SEQ. ID NO. 1.

US Patent 6,194,152
7. A method of detecting tumor cells in a tissue sample, comprising

(a) amplifying ***nucleic*** acids generated from said sample by polymerase chain reaction (PCR) using two primers, where said two primers are designed to selectively amplify a ***nucleic*** acid sequence which encodes a prostate-derived tumor antigen, said ***nucleic*** acid sequence presented as nucleotides 43 to 3327 of SEQ ID NO: 14; and

(b) detecting the presence of amplification products that ***correspond*** to said sequence or amplified portions thereof.

US Patent 6,107,044

14. The method of claim 1, further comprising detecting the separated ***nucleic*** acid fragments, thereby providing signals corresponding to the detected ***nucleic*** acid fragments and recording the presence of the signals.

15. The method of claim 14, further comprising analyzing the resulting recorded signal to distinguish between different sets of ***nucleic*** acid fragments in the plurality of sets of ***nucleic*** acid fragments.

16. The method of claim 15, wherein the analyzing step comprises determining an average peak height for a plurality of the signals.

17. The method of claim 15, wherein the analyzing step comprises determining an average peak height for a plurality of the signals and determining the relative position of a plurality of the plurality of signals.

18. The method of claim 17, wherein the sets of nested ***nucleic*** acid fragments ***correspond*** to a sequence of a target ***nucleic*** acid, the method further comprising converting the average peak height and relative position for the plurality or a plurality of signals into a ***nucleic*** sequence corresponding to the sequence of the target ***nucleic*** acid.

US Patent 6,107,031

1. A method for screening for the presence of an organism for which a nucleotide sequence is not known and for confirming that said nucleotide sequence is not known, comprising the steps of:

sequencing all the ***nucleic*** acid in a sample containing ***nucleic*** acid from at least two different genomes;

comparing an entire nucleotide sequence obtained in said sequencing step to a plurality of nucleotide sequences from known organisms;

identifying the presence of the organism for which a nucleotide sequence is not known by finding a continuous run of nucleotide sequence from said sample that does not ***correspond*** to a known nucleotide sequence; and

confirming the continuous run of nucleotide sequence as a nucleotide sequence of the organism for which the nucleotide sequence was not known.

US Patent 6,025,167

1. A non-naturally occurring enzymatic ribonucleic acid molecule comprising ribonucleotides, capable of cleaving a phosphate ester bond by transesterification in a separate RNA molecule at a predetermined site in a single-stranded target nucleotide sequence within said separate RNA molecule, which enzymatic ribonucleic acid molecule comprises:

(i) an enzymatic portion having endonuclease activity independent of any protein in vitro; and

(ii) a substrate binding portion capable of binding with the target nucleotide sequence in said separate RNA; wherein said substrate binding portion is modified at one or more positions such that specificity of said ***nucleic*** acid is changed, and wherein said enzymatic ribonucleic acid lacks a nucleotide base sequence which binds to said substrate binding portion.

23. The enzymatic ribonucleic acid molecule of claims 1-3, said enzymatic ribonucleic acid molecule being chemically synthesized to ***correspond*** to naturally occurring RNA wherein the naturally-occurring cleavage site of said naturally-occurring RNA has been deleted.

US Patent 5,962,223

1. A kit for determining the presence or absence of a target polynucleotide sequence in a ***nucleic*** acid sample, said kit comprising:

a first probe which is complementary to a first region of a target sequence,

a second probe which is complementary to a second region of the target sequence, where said first and second target regions are contiguous with one another, and said first and second probes are capable of being ligated to each other when hybridized to such contiguous first and second target regions,

a third probe which is complementary to a third target region of the target sequence which is continuous with the first target region, such that said second and third target regions ***correspond*** to alternative allelic sequences or to a normal and mutated sequence, and

ligation means capable of ligating first and second probes, or first and third probes, that have hybridized specifically to contiguous target regions to which the first and second probes, or first and third probes, are complementary, respectively.

US Patent 5,866,330

20. A method for detection of gene expression comprising:

cleaving a cDNA sample with a first restriction endonuclease, wherein the endonuclease cleaves the cDNA at a defined position at the 5' or 3' terminus of the cDNA thereby producing defined sequence tags;

isolating the defined sequence tags;

dividing said defined sequence tags into first and second pools;

ligating a first pool of tags with a first oligonucleotide linker having a first sequence capable of hybridizing to an amplification primer and ligating a second pool of tags with a second oligonucleotide linker having a second sequence capable of hybridizing to an amplification primer;

cleaving the tags with a second restriction endonuclease which cleaves at a position outside its recognition sequence;

ligating the two pools of tags to produce a ditag; and

determining the nucleotide sequence of the tag(s), wherein the tag(s) ***correspond*** to a mRNA from an expressed gene.

US Patent 5,756,325

1. A mixed ribo-deoxyribonucleic acid having at most one 3' end and one 5' end, which ***nucleic*** acid further comprises:

a) at least one region of contiguous unpaired bases disposed so that the unpaired region separates the ***nucleic*** acid into a first strand and a second strand connected by said region of contiguous unpaired bases;

b) at least one region of Watson-Crick paired ***nucleic*** acid of at least 15 base pairs in length, in which bases of the first strand ***correspond*** to bases of the second strand, and in which;

c) the first strand comprises a region of at least three contiguous nucleotides comprised of a 2'-OMe ribose, which form a hybrid-duplex within the region of Watson-Crick paired ***nucleic*** acid.

US Patent 5,695,937

18. A method for detection of gene expression comprising:

cleaving a cDNA sample with a first restriction endonuclease, wherein the endonuclease cleaves the cDNA at a defined position in the cDNA thereby producing defined sequence tags;

isolating the defined cDNA tags and forming a first pool of tags;

ligating a first pool of tags with a first oligonucleotide linker having a first enzyme recognition site that allows DNA cleavage at a site distant from the second recognition site:

ligating a second pool of tags with a second oligonucleotide linker having a second enzyme recognition site that allows DNA cleavage at a site distant from the second recognition site;

cleaving the tags with a first and a second tag cleaving restriction endonuclease, wherein the first tag-cleaving restriction endonuclease recognizes a first enzyme recognition site and cleaves at a site distant from the first recognition site and wherein the second tag-cleaving restriction endonuclease recognizes a second enzyme recognition site and cleaves at a site distant from the second recognition site;

ligating the two pools of tags to produce at least one ditag; and

determining the nucleotide sequence of at least one ditag, wherein the ditag(s) ***correspond*** to sequence from an expressed gene.

US Patent 5,693,468

1. A probe comprising an oligonucleotide 10 to 100 nucleotides in length able to hybridize to a Chlamydia trachomatis ***nucleic*** acid target region to form a detectable target:probe duplex under selective hybridization conditions with ***nucleic*** acid from Chlamydia trachomatis, said target region corresponding to, or fully complementary and of the same length to a ***nucleic*** acid corresponding to, a region selected from the group consisting of:

bases 60-105 of E. coli 16S rRNA,

bases 175-210 of E. coli 16S rRNA,

bases 600-635 of E. coli 16S rRNA,

bases 830-870 of E. coli 16S rRNA,

bases 275-320 of E. coli 23S rRNA,

bases 330-365 of E. coli 23S rRNA,

bases 1160-1190 of E. coli 23S rRNA,

bases 1450-1490 of E. coli 23S rRNA,

bases 1510-1545 of E. coli 23S rRNA, and

bases 1710-1750 of E. coli 23S rRNA;

wherein said oligonucleotide comprises a segment of 10 contiguous bases which is at least 75% complementary to a target sequence of 10 contiguous nucleotides present in said target region and said oligonucleotide does not hybridize to ***nucleic*** acid from Chlamydia psittaci ATTC #VR813 to form a detectable non-target:probe duplex under said hybridization conditions.

US Patent 5,691,138

9. A method of detecting the presence of Campylobacter jejuni in a biological sample, comprising the steps of:

(a) contacting said biological sample with a pair of primers, wherein each primer consists of 18 to 30 contiguous nucleotides of a ***nucleic*** acid sequence selected from the group consisting of:

a nucleotide sequence of SEQ ID NO:1;

a nucleotide sequence of SEQ ID NO:2;

a nucleotide sequence fully complementary to SEQ ID NO:1;

a nucleotide sequence fully complementary to SEQ ID NO:2;

a nucleotide sequence which hybridizes with SEQ ID NO:1 under stringent conditions within a temperature range of (Tm--15.degree. C.) to (Tm--20.degree. C.);

a nucleotide sequence which hybridizes with a nucleotide sequence fully complementary to SEQ ID NO:1 under stringent conditions;

a nucleotide sequence which hybridizes with SEQ ID NO:2 under stringent conditions; or

a nucleotide sequence which hybridizes with a nucleotide sequence fully complementary to SEQ ID NO:2 under stringent conditions;

wherein stringent conditions are

hybridizing for 16-18 hours at 65.degree. C. in 6X SSC buffer containing 10% dextran sulfate, a 5X concentrated Denhardt's solution 10 mM EDTA, 0.05% SDS, 100 .mu.g/ml denatured salmon sperm DNA;

washing twice for 10 minutes at 65.degree. C. in 2X SSC, once for 30 minutes at 65.degree. C. in 2X SSC+0.1% SDS and once for 10 minutes at 65.degree. C. in 0.1X SSC; and

detecting hybridization to C. jejuni but not to other Campylobacter species;

(b) amplifying any genomic ***nucleic*** acid sequences of Campylobacter jejuni in said sample; and

(c) detecting the presence of any amplified genomic ***nucleic*** acid sequences.

10. The method of claim 9, further comprsiing the step of (d) verifying that the sequence of any amplified genomic nucleoic acid sequences ***correspond*** to genomic material of Campylobacter jejuni.

US Patent 5,631,129

2. ***Nucleic*** acid primers according to claim 1 wherein the first and the second portions of said autocatalytically replicatable RNA ***correspond*** to complementary strands of an autocatalytically replicatable RNA which is recognized by Q-beta replicase.

US Patent 5,565,350

1. A mixed ribo-deoxyribonucleic acid having at most one 3' end and one 5' end, which ***nucleic*** acid further comprises:

a) at least one region of contiguous unpaired bases disposed so that the unpaired region deparates the ***nucleic*** acid into a first strand and a second strand;

b) connected by said region of contiguous unpaired bases a region of Watson-Crick paired ***nucleic*** acid of at least 15 base pairs in length, in which bases of the first strand ***correspond*** to bases of the second strand, and in which:

c) the first strand comprises a region of at least three contiguous nucleotides comprised of a 2'-O or 2'-OMe ribose, which form a hybrid-duplex within the region of Watson-Crick paired ***nucleic*** acid.

US Patent 5,474,746

1. A full-length cDNA encoding an attenuated, cell culture-adapted, infectious Hepatitis A virus, wherein said cDNA has a ***nucleic*** acid sequence corresponding to HAV HM-175/7 MK-5 except for nucleotides at positions 7027 and 7425, wherein the nucleotides of the cDNA ***correspond*** to those of wild-type HAV HM-175.

US Patent 5,378,606

1. A ***nucleic*** acid probe for the detection of Neisseria gonorrhea, wherein said probe comprises a sequence selected from the group consisting of the sequences shown in SEQ ID NOS: 4 to 15 inclusive, wherein any additional nucleotides which are present in the probe do not change the specific hybridization of said probe and wherein the total length of said probe is at least 14 nucleotides but less than 30 nucleotides.

2. The probe according to claim 1, wherein less than 8 additional nucleotides are at the 5' end, the 3' end or

at both the 5' and the 3' ends.

3. The probe according to claim 1, wherein any additional nucleotides present ***correspond*** to nucleotides present in a natural 23S rRNA gene from which the probes are derived.

US Patent 5,173,294

14. A method for the detection of Haemophilus influenzae comprising:

a) obtaining a sample of tissue, body fluid or secretion;

b) reacting the sample with a probe comprised of a nucleotide sequence synthesized to ***correspond*** to a portion of a gene encoding a Haemophilus influenzae outer membrane protein having a molecular size of from about 15,000 to about 17,000 daltons;

c) detecting interaction between the sample and the probe, said interaction being between the genetic material of Haemophilus influnzae and the probe.

US Patent 5,077,195

17. A method for preparing polypeptides having a minimum complementary peptide binding activity for a polypeptide ligand based on its cellular receptor site comprising the steps of:

ascertaining a second nucleotide sequence of a second nucleotide strand base-pairing with a first nucleotide strand coding for at least a part of a protein portion of a peptide ligand receptor site;

determining any amino acid sequences in the peptide ligand that are homologous to amino acid sequences coded by the second nucleotide sequence when said second sequence is read in a 3' to 5' or 5' to 3' direction;

determining the amino acid sequences of the receptor site for the polypeptide ligand that ***correspond*** to the homologous amino acid sequences of the preceding step; and

preparing a polypeptide comprising at least a portion of at least one of said amino acid sequences of the receptor site.

US Patent 4,987,071

51. An enzymatic RNA molecule having an endonuclease activity independent of any protein, said activity being specific for a nucleotide sequence defining a cleavage site comprising single-stranded RNA in a separate RNA molecule, said enzymatic RNA molecule being chemically synthesized to ***correspond*** to naturally occurring RNA wherein the naturally-occurring cleavage site of said naturally-occurring RNA has been deleted.

US Patent 4,683,195

19. A process for synthesizing a ***nucleic*** acid fragment from an existing ***nucleic*** acid fragment having fewer nucleotides than the fragment being synthesized and two oligonucleotide primers, wherein the ***nucleic*** acid being synthesized is comprised of a left segment, a core segment and a right segment, and wherein the core segment is sufficiently complementary to the nucleotide sequence of said existing ***nucleic*** acid fragment to hybridize therewith, and the right and left segments represent the nucleotide sequence present in the 5' ends of the two primers, the 3' ends of which are complementary to, or sufficiently complementary to hybridize with, the 3' ends of the single strands produced by separating the strands of said existing ***nucleic*** acid fragment, which process comprises:

(a) treating the strands of said existing fragment with two oligonucleotide primers under conditions such

that an extension product of each primer is synthesized which is complementary to each ***nucleic*** acid strand, wherein said primers are selected so as to be sufficiently complementary to the 3' end of each strand of said existing fragment to hybridize therewith, such that the extension product synthesized from one primer, when it is separated from its complement, can serve as a template for synthesis of the extension product of the other primer, and wherein each primer contains, at its 5' end, a sequence of nucleotides which are not complementary to said existing fragment and which ***correspond*** to the two ends of the ***nucleic*** acid fragment being synthesized;

(b) separating the primer extension products from the templates on which they were synthesized to produce single-stranded molecules;

(c) treating the single-stranded molecules generared from step (b) with the primers of step (a) under conditions such that a primer extension product is synthesized using each of the single strands produced in step (b) as a template so as to produce two intermediate double-stranded ***nucleic*** acid molecules, into each of which has been incorporated the nucleotide sequence present in the 5' end of one of the oligonucleotide primers, and two full-length double-stranded ***nucleic*** acid molecules, into each of which has been incorporated the nucleotide sequence present in the 5' ends of both of the oligonucleotide primers;

(d) repeating steps (b) and (c) for a sufficient number of times to produce the full-length double-stranded molecule in an effective amount;

(e) treating the strands of the product of step (d) with two primers so as to lengthen the product of step (d) on both ends; and

(f) repeating steps (a)-(d) using the product of step (d) as the core fragment and two oligonucleotide primers which are complementary to, or sufficiently complementary to hybridize with, the 3' ends of the single strands produced by separating the strands of the product of step (d).